Alterations in the lower urinary tract in neurogenic bladder dysfunction

Neuropathic bladder dysfunction is associated with high pressures during both storage and voiding as a consequence of various mechanisms. This may affect muscle directly, due to increased workload. It may cause an attrition of innervation or trophic factors locally, including loss of individual nerve fibres and loss of diversity of transmitters. Consequently, various alterations in detrusor structure and function and local innervation have been reported. Changes may be compounded by additional factors, such as bladder management methods and recurrent infections. Overall, various stressors of rather differing character can yield a similar overall pattern of abnormal features in the lower urinary tract.

M. J. Drake, Bristol

Physiological stresses on the neuropathic lower urinary tract

The normal bladder represents a low pressure reservoir for storage of urine. The bladder contracts at the time of voiding, but overall pressures during voiding are modest and not sustained for a long duration. In contrast, several changes can increase the pressure during storage and voiding in neurogenic lower urinary tract (LUT) dysfunction, and the exposure to the increased pressures can be protracted. For upper motor neuron lesions, detrusor overactivity is a common feature of neuropathic bladder dysfunction, giving rise to bladder contractions which may be

high amplitude and sustained. For lower motor neuron lesions, particularly those affecting the sacral part of the spinal cord, bladder compliance can be affected, as a consequence of which ongoing filling leads to continuously rising pressure. The classic feature affecting pressures during voiding is detrusor sphincter dyssynergia, where communication between the pontine micturition centre and the sacral centres controlling the LUT is impaired, leading to disco-ordination of their reciprocal activities. Urodynamically, this gives features of interruptions to urinary flow, with each interruption being associated with high detrusor pressures. Other patterns of sphincter dysfunction, such as fixed non-relaxing sphincter dysfunction, can likewise lead to increased pressure during voiding. High pressures during voiding and storage can affect muscle directly, due to the increased workload and altered physical environment. The increased pressure may also impair vascular perfusion. Within the bladder, the innervation is highly sensitive to ischemia and high pressure can be anticipated to impair blood supplies. Thus, people with acquired neurological disease are at risk of a range of potential changes affecting storage and voiding pressures with potentially profound effect on structure and function. People with congenital and perinatal neurological disease may well not develop normal structure and function in the first place.

Influences on lower urinary tract structure and function

The pathophysiological effects of neurological disease on bladder structure and function are complex with an interplay of direct and indirect influences, further compounded by other patient factors (see table 1).

Samples of detrusor muscle taken from neuropathic bladder behave very differently from control specimens, with an increased level of spontaneous activity, including fused tetanic contraction, the latter being a rare feature in normal detrusor muscle from humans.[1] Increased spontaneous activity might reflect an up-regulation of surface muscarinic receptors on detrusor cells, reflected in denervation supersensitivity.[2] In addition, there appears to be increased intercellular muscle-to-muscle communication.[3] This may well allow propagation of excitation, which could give rise to the fused tetanic contractions. Changes in muscle cells might also reflect changes in the overall environment, including cytokines. A range of alterations and cytokines can be anticipated, and up regulation of bradykinin is a notable example.[4]

Ischaemia during obstructed voiding is well-described in animal models.[5] Furthermore ischemia can be seen in human specimens using near infrared spectroscopy.[6] As a very active structure metabolically, innervation could be at particular risk from ischaemia. Denervation is a well-recognised feature of neurological disease, with global denervation being a specific finding in areflexic spinal cord injury specimens and patchy denervation being a more representative pattern in hyperreflexic spinal cord injury samples from humans.[1] It is specifically the terminals nerve endings that are affected, within the detrusor fascicles and in the subepithelial (presumptive afferent) plexus.[7] A general reduction in transmitters co-localised within the nerve fibres is evident, affecting neuropeptide Y[8] and a whole host of transmitters.[1] The nature of neuromuscular transmission,[9] with normally modest levels of non-cholinergic transmission in humans, may change to an increased contribution of atropine-resistant transmission (perhaps mediated by purinergic signalling)–though it is hard to ascertain with current levels of knowledge how this relates to the overall loss of nerve fibres and transmitters.

Structurally, there can be a profound infiltration of connective tissue in neuropathic specimens. In extremes cases, detrusor muscle can be almost completely lost (figure 1). This might reflect alterations in the levels of the specific connective tissue growth factors responsible for morphometric and molecular remodelling of the bladder.[10] Preceding bladder management can easily be anticipated to alter structure and function.[11] Crucial factors will be the pressures generated during storage and voiding, the presence of foreign body in the bladder, and the tendency to recurrent infections. These clearly vary with the different management methods and chronic indwelling urinary catheterisation is regarded by many as substantially predisposing to structural changes in the bladder wall which may well be irreversible. A very wide range of factors influences the predisposition to urinary tract infection in neurogenic bladder.[12] Such

KeyPoints

- High pressure during storage and voiding can directly alter muscle properties, or indirectly influence organ function by attrition of innervation and other cellular structures.
- Secondary influences, such as preceding bladder management, urinary tract infections, and co-morbid conditions, may have additional consequential effects.
- The wide range of pathophysiological processes tends to result in similar appearances of failure of adaptive relaxation (during the storage phase) and impaired voiding contraction.

1. Primary effects of neurological disease; direct denervation, loss of inhibition, altered trophic factors
2. Indirect consequences of neurological disease; urinary tract infections, bladder management method, increased storage pressure, increased voiding pressure
3. Additional patient factors; comorbid diseases, benign prostate obstruction in men, child birth in women

Table 1: Pathophysiological influences

infection represents a further high risk factor in regards to structural bladder changes.

Multiple influences, common outcome

In general terms, the structural changes in neurogenic bladder dysfunction lead to a loss of adaptive relaxation during the storage phase, and impaired active contraction of the bladder during the voiding phase. Numerous influences can give rise to these features, which could broadly be categorised as descending, neurogenic, myogenic and viscoelastic. The descending influences are particularly crucial, since inhibitory influences on the parasympathetic supply to the bladder exert an active suppression of detrusor contractility during storage, and are reversed in the voiding phase to give rise to the detrusor contraction for expulsion. Loss of local innervation will clearly alter the muscle behaviour, though in reality the diversity of transmitters seen in normal bladder is not fully explained and specific roles for the range of transmitters cannot be ascribed on current evidence. Myogenic alterations, reflecting bladder outlet obstruction or denervation, are directly relevant. The influence on interstitial cells may reflect some of the stresses imposed on the nerve supply and muscle, and can be readily anticipated to influence overall bladder function. The trophic influences resulting from altered innervation, epithelium, infection and foreign bodies will impair the ability of active muscle relaxation during storage and forced generation during voiding. The convergent nature of the end point of these disparate mechanisms is illustrated in figure 2. ■

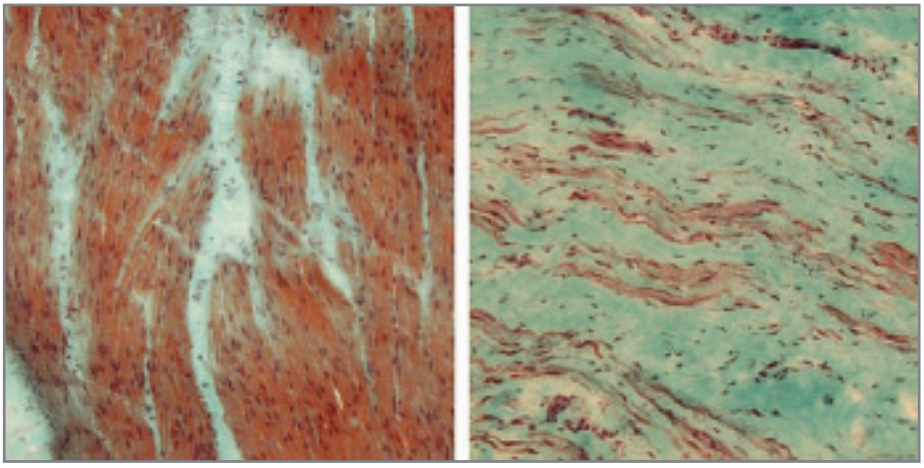

Fig. 1: Normal detrusor muscle (left) compared with the extensive connective tissue infiltration in a person with spinal cord injury (Masson trichrome stain; detrusor pink, connective tissue blue)

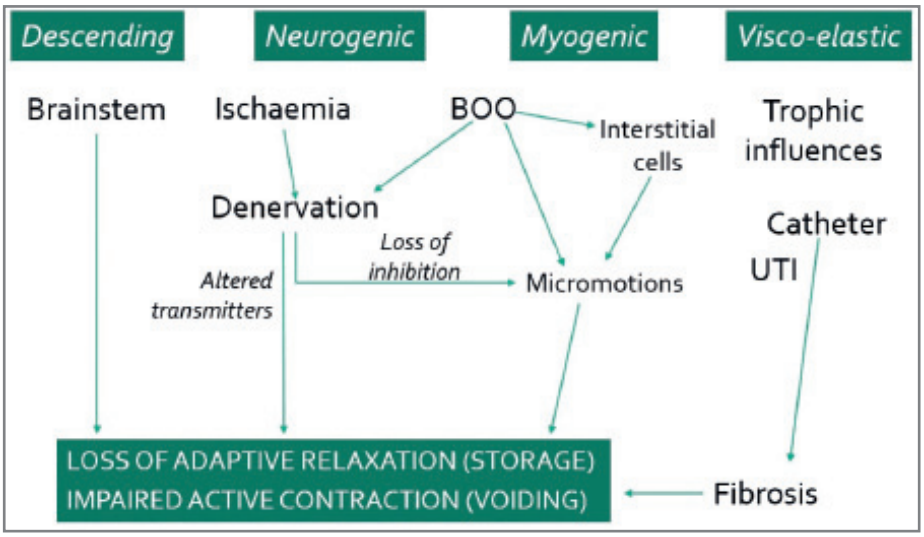

Fig. 2: Diagramatic representation of the convergence of pathophysiological stresses giving rise to common features of storage and voiding dysfunction in the neuropathic lower urinary tract

Literature:

[1] *Drake MJ et al: Structural and functional denervation of human detrusor after spinal cord injury. Lab Invest 2000; 80: 1491-9*

[2] *Brading AF: A myogenic basis for the overactive bladder. Urology 1997; 50: 57-67; discussion 8-73*

[3] *Phe V et al: Involvement of connexins 43 and 45 in functional mechanism of human detrusor overactivity in neurogenic bladder. Urology 2013; 81: 1108 e1-6*

[4] *Forner S et al: Effects of kinin B(1) and B(2) receptor antagonists on overactive urinary bladder syndrome induced by spinal cord injury in rats. Br J Pharmacol 2012; 167: 1737-52*

[5] *Greenland JE et al: Urinary bladder blood flow changes during the micturition cycle in a conscious pig model. J Urol 1996; 156: 1858-61*

[6] *Macnab AJ et al: Ambulant monitoring of bladder oxygenation and hemodynamics using wireless near-infrared spectroscopy. Can Urol Assoc J 2013; 7: E98-E104*

[7] *Drake MJ et al: Innervation of the detrusor muscle bundle in neurogenic detrusor overactivity. BJU Int 2003; 91: 702-10*

[8] *Haferkamp A et al: Distribution of neuropeptide Y-containing nerves in the neurogenic and non-neurogenic detrusor. BJU Int 2006; 97: 393-9*

[9] *Burnstock G: Purinergic cotransmission. Exp Physiol 2009; 94: 20-4*

[10] *Altuntas CZ et al: Connective tissue and its growth factor CTGF distinguish the morphometric and molecular remodeling of the bladder in a model of neurogenic bladder. Am J Physiol Renal Physiol 2012; 303: F1363-9*

[11] *Drake MJ et al: Prospective evaluation of urological effects of aging in chronic spinal cord injury by method of bladder management. Neurourol Urodyn 2005; 24: 111-6*

[12] *Vasudeva P et al: Factors implicated in pathogenesis of urinary tract infections in neurogenic bladders: Some revered, few forgotten, others ignored. Neurourol Urodyn 2013 Mar 4. doi: 10.1002/nau.22378. [Epub ahead of print]*

Author:
Marcus J. Drake
School of Clinical Sciences, University of Bristol, Bristol, UK